

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number  
**WO 2004/005245 A1**

(51) International Patent Classification<sup>7</sup>: **C07C 319/18**,  
319/20, 323/60, C07D 231/44

SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,  
UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:  
PCT/EP2003/008212

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date: 30 June 2003 (30.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
02356131.9 5 July 2002 (05.07.2002) EP

#### Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

(71) Applicant (for all designated States except US): **BAYER CROPSCIENCE S.A.** [FR/FR]; 55 avenue René Cassin, CP 106, F-69266 LYON CEDEX 09 (FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANCEL, Jean-Erick** [FR/FR]; 14 rue Lucien Begule, F-69230 SAINT GENIS LAVAL (FR). **VIDAL, Joëlle** [FR/FR]; 22 rue Jean Guéhenno, F-35700 RENNES (FR).

(74) Agent: **MERIGEALT, Shona**; BAYER CROPSCIENCE S.A., Département Brevets et Licences, 14-20 rue Pierre Baizet, BP 9163, F-69263 LYON CEDEX 09 (FR).

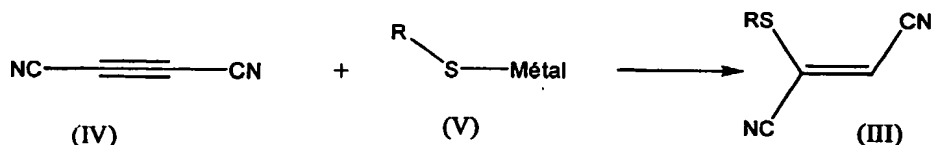
(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,

#### Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF PHENYL PYRAZOLE COMPOUNDS

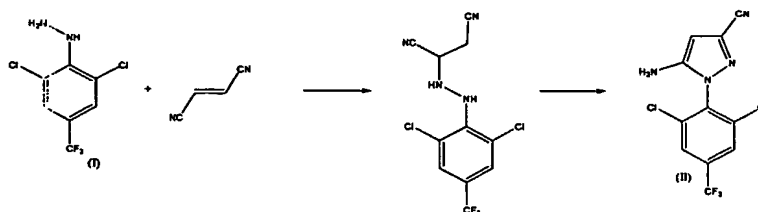


(57) Abstract: A process for the preparation of compound (III) which comprises the reaction between a compound of general formula (V) and dicyano acetylene (IV), said reaction carried out in the presence of water (IV), (V), (III) wherein R is selected from CF<sub>3</sub>, or C<sub>1</sub> to C<sub>6</sub> alkyl M is an alkaline or alkaline-earth metal or silver.

## PROCESS FOR THE PREPARATION OF PHENYL PYRAZOLE COMPOUNDS

The present invention relates to a process for preparing pesticidal intermediates, and to novel 2-arylhydrazono succinonitrile compounds and to 2-arylhydrazino succinonitrile compounds.

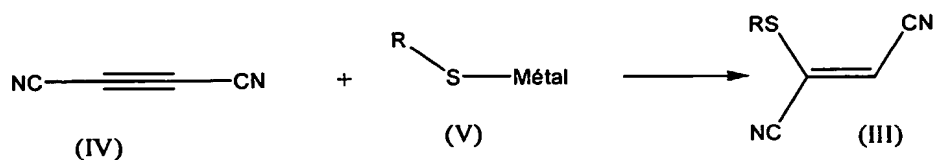
European Patent Publication Nos. 0295117 and 0234119 describe the pesticidally active phenylpyrazole compounds and of 5-amino-1-aryl-3-cyanopyrazole intermediate compounds used in their synthesis. Various methods for preparing these compounds are known, in particular through various intermediate compounds. European Patent No. 0966445 discloses a process for the preparation of a pyrazole compound, formula (II) which is then used to prepare a trifluoromethyl sulfinyl derivative, generally known as fipronil. The process is as shown in the reaction scheme below, starting from an aryl-hydrazine, formula (I):



Unfortunately, this process does not give a direct access to fipronil derivatives, and still requires a further sulphenylation step.

We have now found a method that gives a direct access to sulphenylated derivatives of pyrazole (II).

Accordingly, the present invention provides a process for the preparation of compound (III) which comprises the reaction between a compound of general formula (V) and dicyano acetylene of formula (IV), said reaction carried out in the presence of water



wherein R is selected from CF<sub>3</sub>, or C<sub>1</sub> to C<sub>6</sub> alkyl; and  
M is silver or an alkaline or alkaline-earth metal

5 The preferred compound of formula (V) is when R is trifluoro methyl (CF<sub>3</sub>) and M is silver.

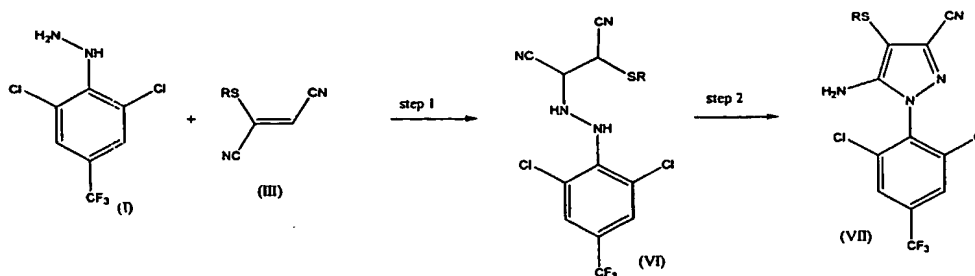
The process of the present invention may be carried out in the presence of a solvent. The solvent is preferably an organic solvent that is miscible with water. Suitable solvents include acetone and tetrahydrofuran.

10 The process may be carried out at a temperature of from -100 to +50°C, preferably from -80 to +20°C. Concentration of the reactants may be from 0.01 to 5 moles per litre of solvent.

The molar ratio of dicyano acetylene to compound of formula (V) is from 5 : 1 to 1 : 5. the preferred molar ratio is 1 : 1.

15 When R of compound (V) is CF<sub>3</sub>, the resulting compound III is a novel compound and thus according to another aspect of the present invention, there is provided a novel compound (III) wherein R is CF<sub>3</sub>

Compound of formula (III) may be used to prepare a known and key intermediate compound of fipronil and according to a further aspect of the present  
20 invention there is provided a process for the preparation of compound (VII) which comprises a first step of reaction of an aryl hydrazine of compound (I) with a compound of general formula (III) to produce an intermediate compound of general formula (VI); and a second step which comprises the oxidation of compound (VI),



wherein R is selected from CF<sub>3</sub>, or C<sub>1</sub> to C<sub>6</sub> alkyl;

Compound of formula (III) is as defined above and may be used in the form of the cis-isomer maleonitrile or the trans isomer fumaronitrile. Optionally a mixture of both isomers may be used. Arylhydrazines of formula (I) are known or may be prepared by known methods.

The preferred compounds of formula (VI) have the same values of R as for compounds of formula (III). Most preferably, compound of formula (VI) is 1-trifluoromethyl thio 2 - (2,6 - dichloro - 4 - trifluoromethyl phenylhydrazino) succinonitrile.

The first step of the process may be carried out in the presence of a solvent. Suitable solvents include polar solvents such as tetrahydrofuran, N-methylpyrrolidone, N,N-dimethylformamide or dimethylsulphoxide. The reaction may alternatively be carried out in the absence of a solvent by heating a mixture of the two reactants, namely compounds of formula (III) and (I).

The first step of the process may also be carried out in the presence of a catalyst such as a tetra-alkylammonium salt for example N-benzyltrimethylammonium hydroxide, or alanine.

The reaction temperature in the first step of the process may be from 0 to 150°C, preferably from 20 to 100°C.

The reaction may be carried out using a molar ratio of a compound of formula (III) to a compound of formula (I) of from 1:10 to 10:1, preferably from 1:1 to 5:1, especially from 1.1 to 1.

When R of compound (VI) is CF<sub>3</sub>, the resulting compound (VI) is a novel compound and thus according to another aspect of the present invention, there is provided a novel compound (VI) wherein R is CF<sub>3</sub>.

Compounds of formula (VI) may be obtained as a mixture of syn and anti isomers and all such forms are embraced by the present invention.

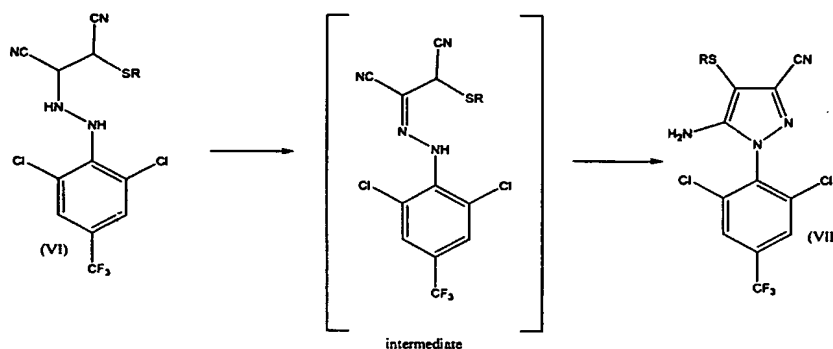
The second step of the process comprises the oxidation of compound of formula (VI) to provide a hydrazone compound. Suitable oxidants for use in the second step include quinones such as benzoquinone, peroxides such as hydrogen peroxide, hypochlorites such as sodium hypochlorite, or an alkali metal hydroxide such

as sodium hydroxide in the presence of air or preferably a metal salt or oxide, for example, cupric chloride or mercuric oxide.

The oxidation reaction may be carried out in the presence of a solvent. Solvents suitable include aromatic halogenated or non-halogenated hydrocarbons such as toluene or chlorobenzene, nitriles such as acetonitrile or amides such as N,N-dimethylformamide.

The oxidation step may be carried out at a temperature of from 20 to 150°C, preferably from 50 to 100°C.

The aforementioned oxidation reaction may be merged with a spontaneous cyclisation of the intermediate hydrazone to produce the corresponding Pyrazole



The present invention will now be illustrated with reference to the following examples:

Example 1: Preparation of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethyl-phenyl) pyrazole

Hydrazine (290 miligrams, 1.2 mmol) was added to a solution of dicyano acetylene (84 mg, 1.1 mmol) in chloroform (2ml). The mixture was stirred for 30 minutes at ambient temperature then heated to 50°C for 3 hours. Purification by flash chromatography on silica gel and crystallisation from dichloromethane/hexane provided a white solid (316 mg; 89%) which was recrystallised in a mixture of hexane/toluene (ratio 2/1) to give the title compound (288 mg, 81% yield).

Example 2 : Preparation of 1,2-Dicyano-1-(trifluoromethylthio)ethene

A solution of  $\text{CF}_3\text{SAg}$  (836 mg; 4mmol) in 2 ml of acetone chilled to  $-78^\circ\text{C}$  under argon was added to dicyanoacetylene (305 mg; 4 mmol) and water (85 mg) in 4ml of acetone. The resulting mixture was shaken for 12 hours. The mixture was  
5 allowed to reach  $20^\circ\text{C}$ . Purification by flash chromatography on silica gel and crystallization from dichloromethane/hexane provided a mixture of the two isomers of the title compound (275 mg, 39% yield) in the form of a brown oil.

Example 3: Preparation of 1-(2,6-dichloro-4-trifluoromethylphenylhydrazono) 1,2-  
10 dicyano-2-trifluoromethylthio ethane

A mixture of 1,2-Dicyano-1-(trifluoromethylthio)ethene (275 mg; 1.5 mmol), obtained in Example 2, hydrazine (378 mg; 1.5 mmol) and 6ml of tetrahydrofuran was stirred at ambient temperature for 24 hours. Purification by flash chromatography on silica gel and crystallisation from dichloromethane/hexane gave  
15 a light brown solid of the title product (442 mg, 67% yield) in a 60/40 mix of the two isomers. The main isomer was dissolved in chloroform and isolated after suspending in 5ml of  $\text{CHCl}_3$ , filtering and washing (80mg, 12% yield).

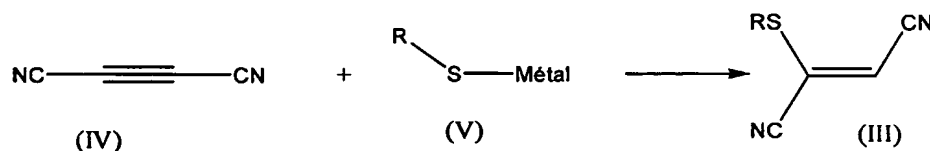
Example 4 Preparation of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoro methyl-  
20 phenyl)- 4-trifluoromethylthio pyrazole

A mixture of 1-(2,6-dichloro-4-trifluoromethylphenylhydrazono) 1,2-dicyano-2-trifluoromethylthio ethane (144 mg; 0.34 mmol), prepared according to Example 3, copper (II) chloride (97 mg; 0.71 mmol), and 4ml of chlorobenzene was stirred for  
25 4 hours at  $100^\circ\text{C}$ . The solvent was then evaporated under vacuum. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and the solution was washed by an aqueous solution of 1% ammonia in water. The product was dried over sodium sulphate, and solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel and crystallization from dichloromethane/hexane gave a white solid (105 mg;  
30 73% yield). The product was then recrystallized in a hexane/toluene mixture to provide a light brown powder (93 mg; 65% yield), melting point  $163^\circ\text{C}$ . A second

recrystallization provided a white powder of the title product with a melting point 165°C .

## CLAIMS

1. A process for the preparation of compound (III) which comprises the reaction between a compound of general formula (V) and dicyano acetylene (IV),  
5 said reaction carried out in the presence of water

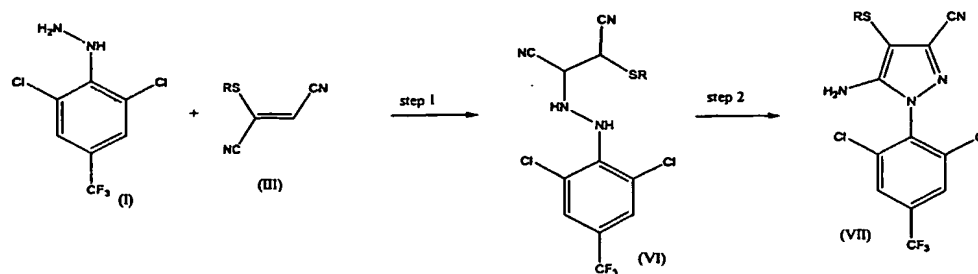


wherein R is selected from CF<sub>3</sub>, or C<sub>1</sub> to C<sub>6</sub> alkyl  
M is an alkaline or alkaline-earth metal or silver

10

2. A process as claimed in claim 1 wherein R is CF<sub>3</sub> and M is silver
3. A process as claimed in claim 1 or claim 2 carried out in the presence of an organic solvent which is miscible with water.
4. A process as claimed in claim 3 in which the solvent is acetone or  
15 tetrahydrofuran.
5. A process as claimed in any one of the preceding claims carried out at a temperature of from -100 to +50°C
6. A process as claimed in any one of the preceding claims carried wherein the molar ratio of dicyano acetylene to compound of formula (V) is from 5:1 to 1:5.
- 20 7. Novel compound according to general formula (III) as defined in claim 1 wherein R is CF<sub>3</sub>
8. A process for the preparation of compound (VII) which comprises a first step of reaction of an aryl hydrazine of compound (I) with a compound of general formula (III) to produce an intermediate compound of general formula (VI), and a  
25 second step which comprises the oxidation of the compound (VI), according to the reaction scheme below





where R is a selected from CF<sub>3</sub> or C<sub>1</sub> to C<sub>6</sub> alkyl.

9. A process as claimed in claim 8 wherein the compound of formula (VI) is 1-trifluoromethyl thio 2 - (2,6 - dichloro - 4 - trifluoromethyl phenylhydrazino) succinonitrile.

10. A process as claimed in claim 8 or claim 9 carried out in the presence of a polar solvent selected from tetrahydrofurane, N-methylpyrrolidone, N,N-dimethylformamide and dimethylsulphoxide

11. A process as claimed in any one of claim in 8 to 10 carried out in the presence of a catalyst selected from N-benzyltrimethylammonium hydroxide, or alanine.

12. A process as claimed in any one of claim in 8 to 11 carried out at a temperature of from 0 to about 150°C

13. A process as claimed in any one of claim in 8 to 12 wherein the molar ratio of compound of formula (III) to compound of formula (I) is from 1:10 to 10:1.

14. A process as claimed in any one of claims 8 to 13 wherein the second step is carried out in the presence of a quinone, a peroxide, a hypohalite or an alkali metal hydroxide

15. A process as claimed in any one of claims 8 to 14 wherein the second step is carried out in the presence of air and optionally a metal salt or oxide

16 A process as claimed in any one of claims 8 to 15 wherein the second step is carried out in the presence of an aromatic halogenated or non-halogenated hydrocarbon solvent.

17 A process as claimed in any one of the claims 8 to 16 wherein the second step is carried out at a temperature of from 20 to 150°C

18. Novel compound according to general formula (VI) as defined in claim 1 wherein R is CF<sub>3</sub>

# INTERNATIONAL SEARCH REPORT

International Classification No

PCT/EP 03/08212

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C07C319/18 C07C319/20 C07C323/60 C07D231/44		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. TURPIN, ET AL.: "Préparation et étude en effet Faraday de quelques esters et du dinitrile de l'acide acétylène-dicarboxylique ainsi que leurs composés d'addition avec les thiols" COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L'ACADEMIE DES SCIENCES, vol. 256, 1963, pages 1712-1714, XP002260946 GAUTHIER-VILLARS, MONTREUIL, FR page 1712, paragraph 4 ----- -/--	1
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *8* document member of the same patent family		
Date of the actual completion of the international search 17 November 2003		Date of mailing of the international search report 03/12/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer English, R

# INTERNATIONAL SEARCH REPORT

International Publication No

PCT/EP 03/08212

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	V.N. KOPRANENKOV, ET AL.: "Phthaloyanines and related compounds. XVI. Synthesis and electronic absorption spectra of amino-, alkoxy-, and alkylthio-substituted porphyrazines" JOURNAL OF GENERAL CHEMISTRY OF THE USSR, vol. 15, no. 4, pt. 1, April 1979 (1979-04), pages 962-967, XP008011376 Consultants Bureau, New York, US page 965, line 17 - line 21	1
A	A.B. BEELER, ET AL.: "Synthesis of fipronil sulphide, an active metabolite, from the parent insecticide fipronil" TETRAHEDRON LETTERS, vol. 42, no. 32, 6 August 2001 (2001-08-06), pages 5371-5372, XP004254962 Elsevier Science Publishers, Amsterdam, NL ISSN: 0040-4039 the whole document	8
A	D. HAINZL, ET AL.: "Mechanisms for selective toxicity of fipronil insecticide and its sulphone metabolite and desulphinyl photoproduct" CHEMICAL RESEARCH IN TOXICOLOGY, vol. 11, no. 12, 7 November 1998 (1998-11-07), pages 1529-1535, XP002261004 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US scheme 2	8
A	EP 0 966 445 B (AVENTIS CROPSCIENCE) 25 July 2001 (2001-07-25) cited in the application the whole document	8

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/08212

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6 (in part), 7, 8-17 (in part), 18

Three-step process for the preparation of  
4-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-  
trifluoromethylthiopyrazole starting from dicyanoacetylene  
as well as the intermediates  
1,2-dicyano-1-trifluoromethylthioethene and  
1-(2,6-dichloro-4-trifluoromethylphenylhydrazono)-1,2-  
dicyano-2-trifluoromethylthioethane  
---

2. claims: 1-6 (in part)

Process for the preparation of 1-alkylthio-1,2-dicyanoethene  
derivatives  
---

3. claims: 8-17 (in part)

Two-step process for the preparation of  
4-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-  
alkylthiopyrazole derivatives  
---

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Publication No

PCT/EP 03/08212

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0966445	B	29-12-1999	
		GB 2324086 A	14-10-1998
		AT 203521 T	15-08-2001
		AU 744505 B2	28-02-2002
		AU 6823298 A	22-09-1998
		BG 103751 A	31-05-2001
		BR 9807988 A	08-03-2000
		DE 69801214 D1	30-08-2001
		DE 69801214 T2	08-11-2001
		DK 966445 T3	24-09-2001
		EA 1777 B1	27-08-2001
		EP 0966445 A1	29-12-1999
		GR 3036282 T3	31-10-2001
		HU 0002159 A2	28-10-2000
		JP 2001513792 T	04-09-2001
		NZ 337840 A	29-06-2001
		SI 966445 T1	31-10-2001
		SK 119199 A3	13-03-2000
		US 6084105 A	04-07-2000
		US 6258973 B1	10-07-2001
		CN 1421439 A	04-06-2003
		CN 1103759 B	26-03-2003
		WO 9839302 A1	11-09-1998
		ES 2158676 T3	01-09-2001
		PL 335443 A1	25-04-2000
		PT 966445 T	30-11-2001
		TR 9902141 T2	21-04-2000
		ZA 9801611 A	25-08-1999